

Managing food allergy: protocol for a rapid systematic review

Prepared by:

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BACKGROUND

Recent estimates suggest that around 17 million people in Europe suffer from allergies triggered by foods such as milk, eggs, peanuts, tree nuts or seafood, and an increasing number are seeking treatment through primary care and hospital emergency departments.¹ Food allergies can have a significant effect on people's quality of life and physical functioning and can also be costly in terms of medical visits and treatments.² With such high social and economic costs, it is important to ensure that effective, evidence-based treatments are available.

The European Academy of Allergy and Clinical Immunology (EAACI) is developing guidelines about what constitutes an effective treatment. As part of the guidelines development process, a systematic review is planned to examine published research about the management of food allergy in adults and children.

Aims

The aim of this systematic review will be to:

- examine what pharmacological and non-pharmacological interventions have been researched to manage the symptoms of food allergy in individuals (ie acute treatment)
- examine what pharmacological and non-pharmacological interventions have been researched to manage longer-term outcomes in individuals such as tolerance and coping (ie longer term management)
- where possible, quantify the extent to which such approaches may be effective

Scope

The umbrella term “food hypersensitivity” is used to describe any adverse reaction to food.³ The term “food allergy” refers to the subgroup of food-triggered reactions in which immunological mechanisms have been implicated, whether IgE-mediated, non-IgE-mediated or involving a combination of IgE- and non-IgE-mediated etiologies.⁴ All other reactions to food that have sometimes been referred to as “food intolerance” constitute non-allergic food hypersensitivity reactions and are outside the focus of this enquiry.

The topic of food allergy is complicated however, by the fact that IgE-mediated reactions can manifest as angioedema, urticaria, atopic eczema/dermatitis, oral allergy syndrome and anaphylaxis, for example. Non-IgE-mediated immunological reactions result from activation of other immunological pathways (e.g., T-cell mediated) and can manifest as atopic eczema/dermatitis, gastro-esophageal reflux disease, food protein-induced enterocolitis, proctocolitis, and enteropathy syndromes. The contemporary definition of food allergy thus includes several clinical entities with different pathophysiologies resulting from exposure to different foods.⁵ Appendix 1 lists the potential manifestations of food allergy included in the review.

The clinical management of food allergy includes strategies to minimize the risk of further reactions, primarily through education and behavioral approaches to avoid allergens and dietary modification, and approaches to improve outcomes if a further reaction does occur through pharmacological and non-pharmacological management strategies. There is also growing interest in the effectiveness of potential immuno-modulatory treatment approaches, including sublingual and oral immunotherapy.² The review will synthesize evidence about the effectiveness of these management approaches for individuals. Interventions at a community, organizational or societal level, such as food labeling or regulation will not be included.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the *EAACI Guideline for Food Allergy and Anaphylaxis*, and this systematic review is one of seven inter-linked evidence syntheses that are being undertaken in order to provide a state-of-the-art synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis and clinical management and impact on quality of life, which will be used to inform clinical recommendations.

METHODS

Inclusion criteria

We have conceptualized the review to incorporate the interventions, study designs and outcomes shown in Figure 1.

Figure 1: Conceptualization of systematic review on the management of food allergy

Managing food allergy		
<u>Interventions</u>	<u>Study designs</u>	<u>Outcomes</u>
<ul style="list-style-type: none"> * treatments targetting acute symptoms * treatments targetting longer term management 	<ul style="list-style-type: none"> * systematic reviews with or without meta-analysis * randomized controlled trials * quazi controlled trials, controlled clinical trials, controlled before and after studies and interupted time series 	<ul style="list-style-type: none"> * effectiveness for symptom control * improvements in clinical markers * effectiveness for food tolerance * coping / anxiety / quality of life * safety of treatment * cost-effectiveness

Study designs eligible for inclusion in the review comprise:

- systematic reviews with or without meta-analyses
- randomized controlled trials
- quazi-randomised controlled trials and controlled clinical trials (defined as studies where the comparison group is not fully randomized)
- controlled before and after studies (only where a clearly defined comparison group is available prospectively) and interrupted time series studies (where measures are taken during at least three timepoints before and at least three time points after intervention)

We suspect that there will be limited information available from systematic reviews and randomized trials, so we have opted to include lower forms of evidence where non-random allocation of patients has occurred.⁶ Studies already included in other systematic reviews will also be eligible for quality appraisal and inclusion in this review. Only research published as full papers will be eligible for inclusion. Where repeated reports of the same study are identified, the most up to date or detailed will be included.

Exclusion criteria

The following material will be excluded from the review:

- non-systematic reviews, discussion papers, non-research letters and editorials
- qualitative studies
- case studies, case series, non controlled before and after studies and other lower quality designs
- animal studies
- abstracts and studies not available in full form
- unpublished material
- studies about anaphylaxis (as these are covered in another review in the series)

Search strategy

We will search the following databases:

- Cochrane Library including,
 - Cochrane Database of Systematic Reviews (CDSR)
 - Database of Reviews of Effectiveness (DARE)
 - CENTRAL (Trials)
 - Methods Studies
 - Health Technology Assessments (HTA)
 - Economic Evaluations Database (EED)
- MEDLINE (OVID)
- Embase (OVID)
- CINAHL (Ebscohost)
- ISI Web of Science (Thomson Web of Knowledge)
- TRIP Database (web www.tripdatabase.com)
- Clinicaltrials.gov (NIH web)

A highly sensitive search strategy has been developed, and validated study design filters will be applied to retrieve all articles pertaining to the management of food allergy from electronic bibliographic databases.

To retrieve systematic reviews, we will use the systematic review filter developed at McMaster University Health Information Research Unit (HIRU) (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews).

To retrieve randomized controlled trials, we will apply the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format from Chapter 6 of the Cochrane Handbook.⁷ To retrieve non-randomized studies such as interrupted time-series (ITS), controlled before-and-after (CBA) studies and controlled clinical trials (CCT), we will use the Cochrane Effective Practice and Organisation of Care (EPOC) filter Version 2.4 from the EPOC Group (<http://epoc.cochrane.org/literature-searching-systematic-reviews>).⁸

The search strategy has been developed on OVID MEDLINE and then adapted for the other databases (see Appendix 2 for full search strategies). In all cases the databases will be searched from inception to September 30, 2012. All references will be imported into an EndNote Library and tagged with the name of the database. Additional references will be located through searching the references cited in identified reviews and contacting experts in the field.

We will invite experts who are active in the field from a range of disciplines and geography to comment on our search strategy, and the list of included studies. No language restrictions will be applied and where possible all literature will be translated.

Study selection

Identified titles will be checked independently by two reviewers according to the above selection criteria and categorised as: included, not included and unsure. For those papers in the unsure category we will retrieve the abstract and re-categorize as above. Any discrepancies will be resolved by consensus and if necessary a third reviewer will be consulted. Full text copies of potentially relevant studies will be obtained and their eligibility for inclusion independently assessed. Studies that do not fulfil all of the inclusion criteria will be excluded.

Quality assessment strategy

Quality assessments will independently be carried out on each study by two reviewers. Systematic reviews will be assessed for quality using the relevant Critical Appraisal Skills Programme Tool (CASP).⁹ We will assess the risk of bias of studies eligible for the review using the criteria suggested by EPOC.¹⁰ Randomized controlled trials, controlled clinical trials and controlled before and after studies will be assessed for generation of allocation sequence, concealment of allocation, baseline outcome measurements, baseline characteristics, incomplete outcome data, blinding of outcome assessor, protection against contamination, selective outcome reporting and other risks of bias. For interrupted time series designs we will also assess the independence of the intervention from other changes, the pre-specified shape of the intervention and whether the intervention was likely to affect data collection. Our quality assessments will draw on the principles incorporated into the Cochrane EPOC Group guidelines for assessing intervention studies¹¹ and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for assessing observational studies.¹²

Analysis, data synthesis and reporting

Data will be independently extracted onto a customized data extraction sheet by two reviewers, and any discrepancies will be resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer.

A descriptive summary with data tables will be produced to summarize the literature. A narrative synthesis of the data will be undertaken. If clinically and statistically appropriate, meta-analysis using either fixed-effect or random-effects modeling may be undertaken for potentially useful interventions using methods suggested by Agresti and Coul.¹³ The PRISMA checklist will be used to guide the reporting of the systematic review.¹⁴

Appendix 1: Potential manifestations of food allergy eligible for inclusion

Food allergy is complex and may manifest as other pathologies. As well as food allergy per se, studies of the following pathologies are eligible for inclusion, as long as there is suspicion of food allergy and the intervention focuses on addressing dietary or food-related issues.

Pathology	Disorder
IgE-mediated (acute-onset)	Acute urticaria/angioedema Contact urticaria Oral allergy syndrome (pollen-associated food allergy syndrome) Allergic asthma/ wheeze Atopic eczema/dermatitis Immediate gastrointestinal hypersensitivity such as vomiting and diarrhoea
Cell-mediated (delayed onset/chronic)	Food protein induced gastroenteropathy Food protein-induced enterocolitis syndrome Food protein-induced allergic proctocolitis Atopic eczema/dermatitis Allergic contact dermatitis Heiner syndrome
Combined IgE and cell-mediated (delayed onset/chronic)	Atopic eczema/dermatitis Eosinophilic esophagitis Eosinophilic gastroenteritis

Appendix 2: Search strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp Food Hypersensitivity/
2 food allerg*.mp.
3 food hypersensitivity.mp.
4 food hypersensitivities.mp.
5 allergy, food.mp.
6 or/1-5
7 (rat or rats or cow or cows or chicken? or horse or horses or mice
8 or mouse or bovine or animal?).ti.
9 exp animals/ not humans.sh.
10 7 or 8
11 6 not 9
12 MEDLINE.tw.
13 systematic review.tw.
14 meta analysis.pt.
15 or/11-13
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab.
19 placebo.ab.
20 clinical trials as topic.sh.
21 randomly.ab.
22 trial.ti.
23 or/15-21
24 intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or
25 community or complex or DESIGN\$ or doctor? or educational or
26 family doctor? or family physician? or family practitioner? or
27 financial or GP or general practice? or hospital? or impact? or
28 improv\$ or individuali?e? or individuali?ing or interdisciplin\$ or
multicomponent or multi-component or multidisciplin\$ or multi-
disciplin\$ or multifacet\$ or multi-facet\$ or multimodal\$ or multi-
modal\$ or personali?e? or personali?ing or pharmacies or
pharmacist? or pharmacy or physician? or practitioner? or
prescrib\$ or prescription? or primary care or professional\$ or
provider? or regulatory or regulatory or tailor\$ or target\$ or team\$
or usual care)).ab.
(pre-intervention? or preintervention? or "pre intervention?" or
post-intervention? or postintervention? or "post
intervention?").ti,ab.
(hospital\$ or patient?).hw. and (study or studies or care or health\$
or practitioner? or provider? or physician? or nurse? or nursing or
doctor?).ti,hw.
demonstration project?.ti,ab.
(pre-post or "pre test\$" or pretest\$ or posttest\$ or "post test\$" or
(pre adj5 post)).ti,ab.
(pre-workshop or post-workshop or (before adj3 workshop) or
(after adj3 workshop)).ti,ab.

29 trial.ti. or ((study adj3 aim?) or "our study").ab.
30 (before adj10 (after or during)).ti,ab.
("quasi-experiment\$" or quasiexperiment\$ or "quasi random\$" or
quasirandom\$ or "quasi control\$" or quasicontrol\$ or ((quasi\$ or
experimental) adj3 (method\$ or study or trial or
31 design\$))).ti,ab,hw.
32 ("time series" adj2 interrupt\$).ti,ab,hw.
(time points adj3 (over or multiple or three or four or five or six or
seven or eight or nine or ten or eleven or twelve or month\$ or
hour? or day? or "more than")).ab.
33 pilot.ti.
34 Pilot projects/
35 (clinical trial or controlled clinical trial or multicenter study).pt.
36 (589305)
(multicentre or multicenter or multi-centre or multi-center).ti.
37 (24808)
38 random\$.ti,ab. or controlled.ti.
(control adj3 (area or cohort? or compare? or condition or design
or group? or intervention? or participant? or study)).ab. not
39 (controlled clinical trial or randomized controlled trial).pt.
40 comment on.cm. or review.ti,pt. or randomized controlled trial.pt.
41 or/23-40
42 10 and 14
43 10 and 22
44 10 and 41
45 or/42-44

**Database: Embase Classic+Embase <1990 to 2012 August 20>
Search Strategy:**

Database: Embase Classic+Embase <1947 to 2012 September 17>
Search Strategy:

- 1 exp Food Hypersensitivity/
- 2 food allerg*.mp.
- 3 food hypersensitivity.mp.
- 4 food hypersensitivities.mp.
- 5 allergy, food.mp.
- 6 or/1-5
- 7 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.
- 8 (animal\$ not human\$).sh,hw.
- 9 7 or 8
- 10 6 not 9
- 11 intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or community or complex or DESIGN\$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv\$ or individuali?e? or individuali?ing or interdisciplin\$ or multicomponent or multi-component or multidisciplin\$ or multi-disciplin\$ or multifacet\$ or multi-facet\$ or multimodal\$ or multi-modal\$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib\$ or prescription? or primary care or professional\$ or provider? or regulatory or regulatory or tailor\$ or target\$ or team\$ or usual care)).ab. (172132)
- 12 (pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]
- 13 (10005)
- 14 [or/11-36]
- 15 [or/38-40]
- 16 [or/42-56]
- 17 [or/61-63]
- 18 *food allergy/
- 19 *nutritional intolerance/
- 20 *Food Hypersensitivity/
- 21 ((food\$ or nutrient\$) adj5 (allerg\$ or hypersensitiv\$ or sensitiv\$ or intoleran\$ or reaction\$)).ti,ab.
- 22 oral allerg\$.ti,ab.
- 23 or/17-21
- 24 intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or community or complex or DESIGN\$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv\$ or individuali?e? or individuali?ing or interdisciplin\$ or multicomponent or multi-component or multidisciplin\$ or multi-disciplin\$ or multifacet\$ or multi-facet\$ or multimodal\$ or multi-modal\$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib\$ or prescription? or primary care or professional\$ or provider? or regulatory or regulatory or tailor\$ or target\$ or team\$ or usual care)).ab.

24 (pre-intervention? or preintervention? or "pre intervention?" or post-
 intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]
 (10005)
 (hospital\$ or patient?).hw. and (study or studies or care or health\$ or
 25 practitioner? or provider? or physician? or nurse? or nursing or
 doctor?).ti,hw. (1422994)
 26 demonstration project?.ti,ab.
 (pre-post or "pre test\$" or pretest\$ or posttest\$ or "post test\$" or (pre adj5
 27 post)).ti,ab. (78798)
 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3
 28 workshop)).ti,ab. (665)
 29 trial.ti. or ((study adj3 aim?) or "our study").ab.
 30 (before adj10 (after or during)).ti,ab.
 (time points adj3 (over or multiple or three or four or five or six or seven or
 eight or nine or ten or eleven or twelve or month\$ or hour? or day? or
 "more than")).ab.
 31 pilot.ti.
 32 intervention?.ti. or (intervention? adj6 (clinician? or collaborat\$ or
 community or complex or DESIGN\$ or doctor? or educational or family
 doctor? or family physician? or family practitioner? or financial or GP or
 general practice? or hospital? or impact? or improv\$ or individuali?e? or
 individuali?ing or interdisciplin\$ or multicomponent or multi-component or
 multidisciplin\$ or multi-disciplin\$ or multifacet\$ or multi-facet\$ or
 multimodal\$ or multi-modal\$ or personali?e? or personali?ing or
 pharmacies or pharmacist? or pharmacy or physician? or practitioner? or
 33 prescrib\$ or prescription? or primary care or professional\$ or provider? or
 regulatory or regulatory or tailor\$ or target\$ or team\$ or usual care)).ab.
 (pre-intervention? or preintervention? or "pre intervention?" or post-
 34 intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]
 (hospital\$ or patient?).hw. and (study or studies or care or health\$ or
 practitioner? or provider? or physician? or nurse? or nursing or
 35 doctor?).ti,hw.
 36 demonstration project?.ti,ab.
 (pre-post or "pre test\$" or pretest\$ or posttest\$ or "post test\$" or (pre adj5
 37 post)).ti,ab.
 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3
 38 workshop)).ti,ab.
 39 trial.ti. or ((study adj3 aim?) or "our study").ab.
 40 (before adj10 (after or during)).ti,ab.
 (time points adj3 (over or multiple or three or four or five or six or seven or
 eight or nine or ten or eleven or twelve or month\$ or hour? or day? or
 "more than")).ab.
 41 pilot.ti.
 42 (multicentre or multicenter or multi-centre or multi-center).ti.
 43 random\$.ti,ab. or controlled.ti.
 44 review.ti. [EM]
 45 *experimental design/ or *pilot study/ or quasi experimental study/ [EM]
 46 (5126)
 ("quasi-experiment\$" or quasiexperiment\$ or "quasi random\$" or
 quasirandom\$ or "quasi control\$" or quasicontrol\$ or ((quasi\$ or
 experimental) adj3 (method\$ or study or trial or design\$))).ti,ab. [EM]
 47 (118829)
 48 ("time series" adj2 interrupt\$).ti,ab. [EM]

49 or/23-48
50 meta-analys:.mp.
51 search:.tw.
52 review.pt.
53 or/50-52
54 random\$.tw.
55 factorial\$.tw.
56 crossover\$.tw.
57 cross over.tw.
58 cross-over.tw.
59 placebo\$.tw.
60 (doubl\$ adj blind\$).tw.
61 (singl\$ adj blind\$).tw.
62 assign\$.tw.
63 allocat\$.tw.
64 volunteer\$.tw.
65 crossover procedure/
66 double blind procedure/
67 randomized controlled trial/
68 single blind procedure/
69 or/54-68
70 22 and 49
71 22 and 53
72 22 and 69
73 or/70-72
74 73 not 9

Database: CINAHL Search Strategy:

S9	S1 or S8
S8	S6 and S7
S7	S4 or S5
S6	S2 or S3
S5	AB allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S4	TI allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction
S3	AB food or nutrient
S2	TI food or nutrient
S1	(MM "Food Hypersensitivity")

Database: ISI Web of Science: Science Citation Index, Conference Proceedings Citation**Search strategy:**

2

Topic=(food or nutrient) AND Topic=(allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)

Refined by: Web of Science Categories=(ALLERGY OR IMMUNOLOGY) AND Document Types=(PROCEEDINGS PAPER OR MEETING ABSTRACT)

Databases=CPCI-S Timespan=All Years

Lemmatization=On

1

Topic=(food or nutrient) AND Topic=(allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)

Databases=CPCI-S Timespan=All Years

Lemmatization=On

Database: Cochrane Library**Search strategy:**

#1 MeSH descriptor Food Hypersensitivity explode all trees

#2 (food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*)))

#4 (#1 OR #2)

Database: TRIP Database

Search Strategy: (Advanced search screen)

area:"Allergies and Immunology"

any of these words: food allerg*

Downloaded: Evidence Based Synopses, Systematic Reviews, Guidelines

All years

Database: Clinicaltrials.gov

Search Strategy: (Advanced search screen)

Conditions: food allergy or food intoleran* or food reaction or food hypersensitiv* or food sensitiv*

all years

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